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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,689	01/29/2001	Chunhua Yan	CL001079	5442

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/770,689	Yan et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4, 8, 9, 13, and 24-29* is/are pending in the application.

4a) Of the above, claim(s) *13* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4, 8, 9, and 24-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Arguments

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action

2. Claims 4, 8, 9, 13 and 24-29 are pending. Claim 13 remains withdrawn from consideration. Claims 4, 8, 9 and 24-29 are under consideration.

3. The rejection of claims 4, 8, 9 and 24-29 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility is maintained for reasons of record.

Claims 4, 8, 9 and 24-29 are drawn to isolated nucleic acids which encode the ras-like protein of the instant invention (SEQ ID NO:2). The specification discloses that the instant ras-like protein is related to the Nadrin protein which is a neuron-specific, developmentally regulated GTPase-activating protein that is important in regulating calcium-dependent exocytosis (page 5, lines 8-10). The specification asserts that the disclosed novel human ras-like protein is useful in the diagnosis, prevention and treatment of inflammation and disorders associated with cell proliferation and apoptosis (page 5, lines 19-22). The specification asserts that said ras-like protein is useful in assays such as high throughput screening to determine the biological activity of the protein, as a reagent in assays to quantitatively determine levels of the protein in biological fluids, and as markers for tissues in which the protein is preferentially expressed, either constitutively or at a particular stage of development, tissue differentiation or disease state. The specification asserts that the ras-like protein can be used to elicit an immune response or to raise antibodies, or to identify a ligand binding partner so as to develop a system to identify inhibitors of the binding interaction (page 17, lines 12-23).

The asserted utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the ras-like protein of the instant invention. The use of said ras-like protein as a reagent to identify the biological activity of the protein, such as in a high throughput analysis, or in the raising of antibodies to detect the expression of the protein itself, or in assays designed to establish a binding partner for the claimed protein represents an experimental use of the protein which is part of the act of invention, and until it has been undertaken, applicant's claimed invention is incomplete.

The DNA of the instant invention and the protein encoded thereby are compounds which share some structural similarity to the Nadrin protein which is a neuron-specific, developmentally regulated GTPase-activating protein that is important in regulating calcium-dependent exocytosis (page 5, lines 8-10). In contrast, the ras-like protein of the instant invention was found by PCR to be expressed in human lymphocytes (figure 1). Further the specification discloses that "It is thought that Nadrin induces cortical actin filament reorganization; cortical actin filaments act as a cortical barrier and must be reorganized for docking and fusion of synaptic vesicles with plasma membranes". Thus, it is clear that one cannot anticipate the function of the ras-like protein of the instant invention, as the expression pattern includes lymphocytic cells in contrast to neurons, and the relevance of the reorganization of cortical actin filaments in lymphocytes is not suggested by the specification or any art of record.

Further, there is no apparent nexus between the asserted utilities of the diagnosis, prevention and treatment of inflammation and disorders associated with cell proliferation and apoptosis (page 5, lines 19-22) and the proposed molecular function of the instant ras-like protein which is related to the Nadrin polypeptide, said polypeptide a putative reorganizer of cortical actin fibers.

The specification further asserts that these potential uses are based primarily on the source of the protein as well as the class/action of the protein (page 17, lines 29-30). The specification states that "Experimental data as provided in figure 1 indicates that the ras-like proteins of the

present invention are expressed in humans in teratocarcinomas (including neuronal teratocarcinomas) umbilical vein endothelial cells, iris, breast tissue, leiomas, uterus, kidney renal carcinoma (ascites), uterus leiosarcomas and fetal heart as indicated by virtual northern blot analysis. In addition, PCR-based tissue screening panels indicates expression in human leukocytes." (Page 18, last paragraph). Virtual northern blot data put forth in figure 1 indicate that a BLAST database search of EST sequences hit on Accession Numbers gi: 10993873, 11003732, 12040806, 10948137, 11303345, 7933255, 10332226, 11643637, 10348166, 4753575. Firstly, the claimed cDNA sequence of SEQ ID NO:1 consists of 3201 nucleotide residues. A data base hit with a EST sequence consisting of several hundred nucleotides does not guarantee that the claimed sequence of 3201 nucleotides is represented by that EST. Secondly, on examination of the annotations associated with each of the Accession Numbers it is noted that none of the EST sequuences were derived from subtracted libraries. Thus, it cannot be ascertained if the EST of the teratocarcinomas are present in the corresponding normal tissues, or if the EST of the kidney renal sarcoma was present in normal renal cells. Furthermore, it appears that the EST of the uterus leiomyosarcoma could be a tissue specific sequence as it was also found in uterine tissue. It is well known in the art that one cannot rely on a single hit in an EST database to establish the expression pattern of a gene. For instance, Yerushalmi et al (Gene, 2001, vol. 265, pp. 55-60) teach that the gene for ERGL was indicated to be expressed exclusively in the prostate by EST database searching, however, Northern blot hybridization indicated that the gene was also expressed in cardiac atrium, salivary gland, spleen and selective cells in the CNS. In contrast, Caillou et al (Journal of Clinical Endocrinology and Metabolism, 2001, Vol. 86, pp. 3351-3351) reports that Northern blot analysis of different human tissues demonstrated that the LNOX gene was expressed only in the thyroid gland, while blast analysis of EST sequences indicate that the LNOX gene is expressed in non-thyroid tissues. Furthermore, Conklin et al (Briefings in Bioinformatics, 2000, vol. 1, pp. 93-99) teach that the mining of EST databases using only a single member of a protein superfamily is prone to false positive hits as

some proteins contain common domains (page 95, under the heading "Pruning the False Positives"). Thus, as stated above, a single hit in an EST database is not a guarantee that the full length nucleic acid of the instant invention is represented by that hit. It is also noteworthy that another ras-like protein was identified in teratocarcinoma cells by Drivas et al (Identification of Novel ras family genes in a human teratocarcinoma cell line by oligonucleotide screening" In:The ras-Superfamily of GTPases, Lacal and McCormick, Eds., 1993, pages 329-347). However, this ras-like protein was found to be predominantly located in the nuclei of primate cells and not a specific marker for teratocarcinoma (page 343). This data serves to demonstrate that a database hit in an EST library does not establish either an expression pattern for a gene or a function for the encoded protein. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous

to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a protein of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the ras-like protein of the instant application was, as of the filing date, useful for the diagnosis, prevention and treatment of inflammation and disorders associated with cell proliferation and apoptosis (page 5, lines 19-22). Until some actual and specific significance can be attributed to the protein identified in the specification as SEQ ID NO:2, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the ras-like protein of the instant invention, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful.

Applicant argues that the protein of SEQ ID NO:2 has been sufficiently characterized with regard to biological function and significance that one of ordinary kill in the art can use the claimed invention without undue experimentation. This arguments has been considered but not found persuasive, as the requirement for satisfying 35 U.S.C. 101 is not whether one of skill in the art can use the invention without undue experimentation, but whether applicant has asserted a specific, substantial and credible utility or a well-established utility for the claimed invention. For the reasons stated in the previous Office action and re-iterated above, applicant has failed to establish said specific, substantial and credible utility or a well-established utility.

Applicant argues that the protein of SEQ ID NO:2 functions as a Rho-GTPase-activating protein. However, for the reasons stated in the previous Office action and re-iterated above, a specific and substantial utility can not be inferred from membership in this protein family. Applicant argues that the protein of SEQ ID NO:2 is similar to the Nadrin protein which is an example of a RhoGAP protein. However, for the reasons set forth in the previous Office action, no specific, substantial and credible utility is associated with the Nadrin protein. Applicant further argues that analysis of the hypothetical domains of SEQ ID NO:2 indicates that said amino acid sequence contains glycosylation, phosphorylation and myrisolation sites and an aminoacyl-transfer RNA synthetase class I signature. This has been considered but not found persuasive. Possession of a glycosylation, phosphorylation or myrisolation sites, or possession of an aminoacyl-transfer RNA synthetase class I signature are not equated with a specific utility as many other proteins unrelated to the instant invention possess these domains.

Applicant argues that Rho proteins are one of the five subfamilies within the ras superfamily, and Rho proteins are important for controlling signal transduction. Applicant points out that because it is well established in the art that RhoGAP proteins are important for inactivating Rho proteins it t follows that it is well-established that RhoGAP proteins are useful in the diagnosis and prevention of cancer. This has been considered but not found persuasive. Membership in a subfamily of a protein class does not define a specific substantial utility for said

protein, such as the treatment, diagnosis and prevention of cancer, as suggested by the applicant, unless all members of the subfamily were know to have that utility. There is no evidence or any art of record to support the allegation that all members of he RhoGAP subfamily were useful in the treatment, diagnosis and prevention of cancer. Argument with out evidence is not persuasive.

4. The rejection of claims 4, 8, 9 and 24-29 under 35 U.S.C. 112, first paragraph is mainlined for reasons of record. Specifically, since the claimed invention is not supported by either a specific, substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

New Grounds of Rejection

5. Claims 8, 9 and 27-29 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 8 and 27-29 can be interpreted as being drawn to a vector within a human. Claim 9 can be interpreted to be drawn to a host cell comprised within a human. Amendment of the claims to recite "An isolated nucleic acid vector" or "An isolated host cell" would overcome this rejection.

6. In the event that applicant overcomes the rejection under 35 U.S.C. as stated above, the following rejection will apply:

Claim 8, 9 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated expression vector and host cell in vitro, does not reasonably provide enablement for an isolated expression vector or host cell in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. (A)As drawn to an expression vector comprised within a human, or a host cell within a human.

The specification states on 48, that vectors for the delivery of the nucleic acids of the invention include recombinant viral vectors including retro viruses, adenovirus, pox virus. The

specification states on page 42 that the disclosed nucleic acid vectors provide vectors for gene therapy in patients. The claims are clearly intended to encompass methods of gene therapy. However, the specification is not enabling for gene therapy fr the following reasons.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on

Gene Therapy", NIH, 1995) that as of 1995, (two years after the priority date for the instant application) clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B) as drawn to a transgenic animal

The specification states on pages 52-54 that genetically engineered host cells can be used to produce transgenic non-human animals. The specification does not provide guidance in the

making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287, see bridging pages 272-273) and expression is heavily dependent on the site of integration in the host genom, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make the instant recombinant polynucleotides and cells within a transgenic animal.

7. All other rejections and objections as stated in Paper No. 11 are withdrawn.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

May 18, 2003

Karen A. Canella